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# ANNUAL ADDRESS.

## THE CAUSATION OF DIPHTHERIA.

BY

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## THE CAUSATION OF DIPHTHERIA.

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The subject which I have selected for this address is so largely a topic of the day, and fills at present so much space in medical journals, that the main facts which will be here presented must appear familiar to those who have followed recent medical literature. Nevertheless, many of these facts are so new and so important, and the disease to which they relate is one of such great interest, that no apology is needed for bringing before you a brief summary of recent investigations concerning the causation of diphtheria, and the light which these discoveries have shed upon our knowledge of the pathology, prophylaxis and treatment of a disease more dreaded, and justly so, than any other infectious disease always present among us. Although these new discoveries are mainly the results of bacteriological work, it will be my purpose to dwell not so much upon minute bacteriological descriptions, more suitable to the laboratory and to special articles than to a general address of this kind, but rather upon those points which illustrate the application of these discoveries to a fuller and more correct knowledge of the nature, etiology, pathology, diagnosis, prevention and treatment of diphtheria.

The history of our knowledge of diphtheria illustrates the difficulties which we encounter in endeavoring to reach a full understanding of a disease upon the basis of its symptomatology and pathological anatomy alone. Consider for a moment what are some of the uncertain and still much disputed questions concerning this disease.

Is diphtheria primarily local or constitutional in its origin? Are all pseudo-membranous inflammations of the throat, not directly referable to caustic irritants, diphtheria? Is there a purely local, non-contagious pseudo-membranous laryngitis called croup distinguishable from diphtheria? Are the pseudo-membranous anginas secondary to scarlatina, and less frequently to measles and some other infectious diseases identical with diphtheria? Is there any relation between follicular tonsillitis and diphtheria? May diphtheria occur in a mild form as a simple catarrhal inflammation of the throat? Are pneumonia, acute nephritis, suppuration of the glands in the neck, etc., referable to the direct action of the diphtheric virus; in other words, what lesions belong to the disease and what are complications? Shall reliance be placed chiefly upon local or upon general treatment?

These are some of the questions which the most careful study of the clinical history and of the anatomy of diphtheria has not been able to answer clearly and unmistakably. Nor are these matters only of theoretical importance. Referring to the two doctrines of the local and of the constitutional nature of diphtheria, Dr. J. Lewis Smith, one of the most painstaking and profound investigators of this subject in this country, says: "It is a matter of great importance—an importance transcending that of almost any other subject relating to the pathology of this dreadful scourge—that we should ascertain certainly and clearly which of the two prevailing theories is true, since the theory influences practice."

I hope to be able to show in the course of this address that this question, as well as others mentioned, have now been answered "clearly and certainly," and that we are in a position to solve other of the problems still remaining in doubt. All of this gratifying widening and deepening of our knowledge has come from the discovery of the microscopic germ which is the specific cause of diphtheria, and from the study of the singular and interesting properties of this germ. There is, perhaps, no other disease, with the exception of tuberculosis, upon which greater light has been shed by the discovery of its specific cause than upon diphtheria.

Permit me to present to you, in the first place, the evidence that the so-called Klebs-Löffler bacillus is really the specific agent of infection in diphtheria; and then to describe the most important properties of this microörganism, so far as they bear upon the subject of this address.

There are three things especially which have rendered difficult the convincing demonstration that a given microörganism is the specific cause of diphtheria.

The first is the uncertainty as to what shall be called diphtheria, and the possibility that included under this name are various affections which may be due to different causes. Hence it might happen that one investigator studying one class of cases—for instance, the pseudo-membranous anginas associated with scarlet fever, measles, etc.—might obtain results different from another who observed another class of cases. In view of this uncertainty, it is clear that conclusions as to the causation of primary diphtheria should be derived from the investigation of cases which all are agreed in regarding as genuine primary diphtheria. When the etiology of this undoubted class of cases has been determined, we are in a position to examine whether the secondary and other doubtful forms of diphtheria have a different causation or not.

A second difficulty has been not in the demonstration of microörganisms in diphtheria, but rather in the abundance of bacteria present in diphtheritic membranes. Of the various species of bacteria found in the false membranes of diphtheria we must determine which are constantly present and which are inconstant. If we find one species always present in large number and absent in other conditions, the presumption is that this is the specific cause of the disease, and this presumption becomes a certainty if we are able to reproduce experimentally, by inoculation with pure cultures of this germ, a disease in all respects identical with human diphtheria.

Just here we meet the third difficulty, which consists in bringing positive evidence that our experimental disease is in reality identical with human diphtheria. We are accustomed

to regard the fibrinous pseudo-membrane on the mucous membrane of the tonsils, pharynx, and air-passages as the most certain anatomical criterion of diphtheria, but we have long known that it is possible to produce experimentally in animals, by a variety of agencies which have nothing to do with diphtheria, false membranes histologically identical with the diphtheritic membrane. Hence the mere production of a false membrane by the inoculation of a germ suspected to be the cause of diphtheria, although it constitutes weighty evidence, cannot be considered absolutely conclusive that such germ is really the cause of diphtheria. But are there not other anatomical changes in the body characteristic of diphtheria besides the diphtheritic membrane? We owe especially to Oertel the demonstration of the fact that the diphtheric virus is a most peculiar poison to the cells of the human body, and that it produces areas of cell death not only on the surface of mucous membranes, but also in deeper parts, in various lymphatic glands at a distance from the local lesion and in the spleen. These changes can be demonstrated by histological examination. Now, if we find that our suspected germ, besides causing pseudo-membranous inflammations, produces identical foci of cell death; if we find that it injures the kidneys, as we have long known it does in human beings; and if we find that it causes late muscular paralyses resembling the post-diphtheric paralyses which the clinician regards as of such diagnostic value in doubtful cases of sore-throat, then we shall have evidence strong indeed that this germ is the real specific cause of diphtheria.

It is not surprising that all these difficulties were not overcome in the first important publications of Klebs in 1883, and of Löffler in 1884. We owe to Löffler the first bacteriological study of diphtheria by the modern culture methods. Although his work was most valuable and accurate, he was compelled to express himself reservedly as to the significance of the bacillus which we now believe to be the cause of diphtheria. No such complete chain of proof was brought forward as Koch presented in his first memorable publication upon the tubercle bacillus two years previously. Hence it came

about that the Klebs-Löffler bacillus from the first assumed a doubtful status, and that even to-day it is often referred to in writings on diphtheria as only one among many claimants to be regarded as the cause of diphtheria.

I shall not weary you by following the historical path in which obstacle after obstacle has been removed which stood in the way of the full recognition of the Löffler bacillus as the infectious agent of diphtheria, but I shall simply direct you to the goal which has been reached.

It is now established that this bacillus is constantly present in large number in the pseudo-membranes of all cases of primary diphtheria, and that no other species of bacteria is constantly to be found in this situation. The expectation expressed a year ago by Löffler that the results on this point would not be found to be different in this country from those in Europe has been fulfilled by the bacteriological examination by Dr. Abbott and myself of a series of cases of primary diphtheria occurring in Baltimore, in all of which we found the Löffler bacillus, as the only constant organism, as well as by the latest publication of Dr. Prudden. The occurrence of a bacillus, with all the properties of the virulent diphtheric bacillus, in persons not affected with diphtheria is so extremely exceptional that Löffler, notwithstanding years of searching, has been able to find it only once under such circumstances.

The Löffler bacillus can be readily obtained in pure cultivation on artificial media and its properties studied outside of the body. The sum of these properties suffices for its positive and ready identification.

Inoculation of pure cultures of this bacillus is found to be pathogenic for guinea-pigs, cats, pigeons, rabbits, and some other animals. By such inoculation a disease can be reproduced identical in all essential features with human diphtheria, and there is no other species of microörganism known capable of reproducing all of these features. In suitable animals we can cause by inoculating them with the diphtheric bacillus pseudo-membranous inflammations of mucous membranes indistinguishable from those of natural diphtheria, swelling of

adjacent lymphatic glands, multiple ecchymoses, serous transudations, fatty degenerations and other lesions in the kidney and liver, late muscular paralyses, and foci of cell death resembling those in human diphtheria. Upon this last point the investigations in full have not yet been published, but researches have for some time been directed, in the pathological laboratory of the Johns Hopkins University, to the detection of areas of cell-death in the internal organs of the animals inoculated with diphtheria, and I may say here that we have been able to confirm and extend in animals Oertel's researches on this subject in human beings.

By the labors, therefore, of many investigators since Löffler's first publication in 1884, including those of Löffler himself, all of the conditions have been fulfilled for diphtheria which are necessary to the most rigid proof of the dependence of an infectious disease upon a given microörganism, viz: the constant presence of this organism in the lesions of the disease, the isolation of the organism in pure culture, the reproduction of the disease by inoculation of pure cultures, and similar distribution of the organism in the experimental and in the natural disease. We are then justified in calling the Klebs-Löffler bacillus, the bacillus diphtheriæ.

Let us now turn our attention to the most important properties of this bacillus. However great may be the scientific interest of the discovery of the specific germ of an infectious disease, this discovery by itself is after all only the realization of the faith of enlightened physicians that the infectious diseases are all caused by specific living organisms. The practitioner is fully justified in inquiring how this discovery helps him to a better understanding of the disease, to a more certain diagnosis, to a more accurate interpretation of symptoms, to more effective measures of prevention and of treatment. Although these expectations have been met only in part, enough has been accomplished already to show that great practical value has come and is likely to come in still larger measure from the discovery of the bacillus diphtheriæ.

The specific germ of diphtheria is a bacillus, devoid of independent motility, averaging in length about that of the tubercle

bacillus, but thicker than this. It presents itself both in diphtheritic membranes and in cultures often in such bizarre forms that these belong to its most characteristic morphological properties. It grows upon our ordinary culture media, best upon Löffler's blood-serum and bouillon mixture, but it will grow even upon steamed potato. As bearing upon a possible source of infection it is important to note that the bacillus will multiply readily in milk, without altering the appearance of the milk. It does not multiply or it does so only very sluggishly at a temperature below 18° C. (about 64° F.). It is killed by exposure for ten minutes to a temperature of 58° C. (136.4° F.). It is not necessary to describe here in detail the peculiarities of its growth upon the various culture media, although to the bacteriologist these are the guides for the isolation of the bacillus in pure culture. The series of cultures which I here exhibit to you illustrates the characteristic appearances. It suffices here to draw the conclusion that, unlike the tubercle bacillus, the bacillus of diphtheria may readily find conditions outside of the body suitable for its multiplication.

But, as is well known, it is not necessary that an infectious organism should actually propagate itself outside of the body in order to produce ectogenic infection. Such infection may occur if the organism simply preserves its vitality. On this point we know that the diphtheric bacillus, although it forms no spores, is among the more resistant bacilli of the non spore-forming class, withstanding for a long time drying and other influences injurious to the less resistant forms. The specific bacilli have been obtained in cultures made from diphtheric membranes preserved dry in a piece of linen cloth for five months. This ~~prosperity~~ property is in harmony with the experience that rooms, clothing, and other objects may retain for months the diphtheric virus in an active state. As the bacilli diphtheriæ may live for a still longer period in the moist state, and as moist, damp dwellings have long been held to be particularly favorable for the development of diphtheria, it is probable that statements as to the preservation of the diphtheric virus in such situations for a year or more are not without foundation.

Of capital importance is the establishment of the fact that the bacillus diphtheriæ develops only locally at the site of infection, and does not invade the tissues or the circulation. It is found only in the diphtheritic pseudo-membrane, and not even in the subjacent mucous membrane. Indeed, it is only the superficial parts of the false membranes which contain the bacilli. The determination of this fact gives at once a clear and decisive answer to the long-mooted question as to the primarily local or constitutional nature of diphtheria. Diphtheria is, without a doubt, local in its origin. The germ which causes this disease not only makes its first appearance and multiplies where the pseudo-membrane is formed, but it does not subsequently invade the blood and organs. As we shall see later, the constitutional symptoms are due to the reception of a chemical substance or substances of remarkable toxic properties, produced by the local development of the diphtheric bacillus.

This settlement of the controversy as to the local or the constitutional origin of diphtheria is one of the most important outcomes of the bacteriological study of this affection, for the question pertains to a fundamental point in our conception of the disease. Nevertheless, from the point of view from which this controversy has usually been waged, the triumph is, in my opinion, only a partial one for the localists, for, as will be shown later, I believe that there are reasons as strong as ever for the employment of constitutional measures of treatment in combination with the local ones.

From what has already been said we are prepared to consider for a moment in what ways a person affected with diphtheria becomes a source of danger to those around him, and to the locality.

The bacilli diphtheriæ are conveyed from the body in particles of diphtheritic exudation, saliva, and other secretions discharged through the mouth and nose. (It is not necessary to consider the comparatively exceptional localizations of the disease.) In this way the infectious substance may readily become attached to the person and clothing of the

patient, and of those around him, as well as to the bedding, furniture, floor and walls of the room, dishes, and other objects.

Notwithstanding the statements current in nearly all text-books, there is no evidence that the breath of the patient contains the diphtheric germ, except as bits of false membrane or secretion may be mechanically expelled in the act of coughing, hawking, or sneezing. It has been proven experimentally that the expired air is incapable, during ordinary respiration, of detaching bacteria from the moist mucous surfaces over which it passes.

The specific germs are not so readily conveyed by air currents from a diphtheric patient to those near him, as they are, for instance, from a patient with scarlet fever, in which the germs are in all probability thrown off from the surface of the body on light epidermal scales.

Nor are the chances of infection of the sources of supply of drinking-water with the diphtheric bacillus so great as is the case with such diseases as cholera and typhoid fever, in which the stools contain in large number the specific bacteria, and are likely to be disposed of in such a way that under bad sanitary conditions these bacteria may find their way into wells and streams. While there are some accounts intended to show the conveyance of the virus of diphtheria through the drinking water, we do not hear much of this as a source of infection, and it is not likely that it plays an important role, although it is probable that the diphtheric bacillus may sometimes be discharged by the stools.

Diphtheria is one of the infectious diseases the germs of which may be taken into the body by the inspired air. Inasmuch as bacteria cannot, under ordinary conditions, occur as floating matter in the atmosphere until they have been completely dried down so that air currents can detach as dust the little particles to which they adhere, it is evident that only those infectious germs are likely to be conveyed by the air which are not destroyed by complete drying. As has already been mentioned, the diphtheric bacillus withstands for months desiccation which is so injurious to the cholera vibrio and to many other species of bacteria. While,

therefore, we must admit that air-infection with the bacillus of diphtheria is a real and conspicuous danger, it is well to bear in mind that modern bacteriology has taught us the great lesson that the most frequent and important mode of infection is by contact with infected substances. When we consider the manifold ways in which the diphtheric bacilli may be widely distributed, and when we consider the habit of young children—who are the most numerous victims of the disease—of handling everything and of putting everything into their mouths, we are led to appreciate that infection by contact must play the leading part in the transmission of diphtheria.

I will now ask your attention to a brief consideration of the most deadly of all the properties of the bacillus diphtheriæ, namely, the power of producing extraordinarily poisonous chemical substances. That the grave constitutional symptoms of diphtheria are referable to such substances has long been surmised, and as soon as it was found that the bacilli causing diphtheria develop only locally it became certain that toxic substances must be formed. The results of the investigations as to the nature and properties of these substances are not only most important for the etiology of diphtheria, but are among the most significant acquisitions of bacteriology in recent years. We owe these results chiefly to the researches of Roux and Yersin and of Brieger and Fränkel.

If bouillon cultures, four or five weeks old, of the diphtheric bacillus—preferably containing some blood-serum—be sterilized by heating them at temperatures of about 55° C., or if they be deprived of bacteria by filtration through a Chamberland porcelain filter, it is found that the sterilized culture fluid possesses highly poisonous properties when injected, even in small quantity, into animals. The toxic substance is not of a crystallizable, alkaloidal nature of the kind known as a ptomaine or a toxine, for no such substance can be detected in these cultures. The poisonous material, although it has not been separated in a condition of absolute purity, has been shown to be probably of a proteid nature. It is precipitated by alcohol and by saturation with ammonium sulphate and sodium phosphate. It is mechanically

dragged down by fine precipitates, such as those of calcium phosphate. It is soluble in water. Obtained in a state approaching purity it appears as a white, amorphous mass of light specific gravity. In the moist state it loses, in great part or entirely, its poisonous properties when subjected to heat above 60° C., but when dry it stands temperatures of 70° C. It is not volatile, and can be preserved for months at least in the dry state, without loss of its characteristic properties.

Some idea of the extraordinarily poisonous nature of this substance can be obtained from the statement of Roux and Yersin, that four-tenths of a milligramme of the substance (after deducting the weight of the ashes and of the non-poisonous part insoluble in alcohol) obtained by evaporating to dryness the active culture fluid, is sufficient to kill at least eight guinea-pigs, weighing each four hundred grammes, or two rabbits, weighing each three kilogrammes. As the major part of these four-tenths of a milligramme is represented by other substances than the diphtheric poison, it is apparent that the poison must be of appalling potency.

If this poison, or the sterilized culture fluid containing it, be injected into a guinea-pig or rabbit or other susceptible animal, it is found to be capable of producing all of the changes in the body which follow the inoculation of pure cultures of the diphtheric bacilli, with the exception of the pseudo-membrane. For the production of this membrane the bacilli are necessary, but the other lesions, such as the local œdema after subcutaneous injections, the ecchymoses, the serous transudations, the changes in the kidney, liver, and other parts, are observed after the injection of the toxic albumin, as the diphtheric poison is sometimes called, as well as after inoculation with the bacilli. If the animals live sufficiently long, muscular paralyses may develop.

The most remarkable property of this toxic albuminoid substance, or these substances (for we do not know positively that there is only one such substance), is that when injected in a single sufficiently small, but fatal dose, it may produce no apparent disturbance for days, and the death of the

animal may occur many days or even weeks, or months after the injection. This is a quality which we have not been accustomed to attribute to chemical poisons, and it is evidently one of the greatest practical significance. If it is true that the bacilli of diphtheria are capable of producing at the site of their local development poisonous substances which, when at first received into the system, may cause no manifest harm, but which may destroy life perhaps after days, then it is clear that even if we succeed in killing the bacilli in the pseudo-membrane, the individual may still die of toxæmia.

That the bacilli of diphtheria may produce apparently identical toxic proteids in the animal body has been demonstrated. The poisonous proteids are probably allied in their constitution to the poisonous substances found by Weir Mitchell and Reichert in the venom of rattlesnakes and of other serpents, and belong to a group of interesting chemical products now known to be produced by various pathogenic bacteria and other organisms, and which have been and are still being carefully studied, among others, with especial success by Sidney Martin and by Hankin in England. While there is reason to believe that the diphtheric poison is a proteid this view cannot be regarded as established until the poison has been isolated in a state of purity. As we know that the poison can be mechanically dragged down by fine precipitates, it is possible that it is intimately united to the precipitates of albumose without being itself an albumose. Interesting as it might be to tarry longer at this point, we cannot complete this outline sketch of the properties of the diphtheric bacilli without the consideration of certain other important characteristics which they possess, and time admonishes us to hasten on.

It is well known that the character of the symptoms, and especially their gravity, vary in a marked degree not only in different cases of diphtheria, but also in different epidemics. There are epidemics of a mild character, and there are epidemics, such as some of those of recent years in the northwestern part of this country, which sweep away nearly all the children of a neighborhood or a town. In estimating the

value of different methods of treatment, this is a point not always kept sufficiently in view. The question suggests itself whether there is anything known concerning the attributes of the bacillus diphtheriæ which will explain these differences.

As to this point, it is to be said that this bacillus, as obtained in pure culture from different cases of diphtheria, varies in its virulence, as tested upon animals, to a greater degree than any known pathogenic organism. Diphtheric bacilli isolated from different cases of diphtheria, will sometimes kill guinea-pigs by subcutaneous inoculation in twenty-four hours ; in other cases they require two, three, four, even nine days to accomplish this result. From two cases of diphtheria of slight severity recently examined at the Johns Hopkins Hospital, Dr. Abbott obtained in pure culture a bacillus identical in its morphology and its behavior on culture media with the diphtheric bacillus, but incapable of killing guinea-pigs by subcutaneous inoculation. In this respect it resembles the so called pseudo-diphtheric bacillus, but it differs from this organism in having been present in the diphtheritic exudate in large number.

While observations are as yet insufficient to justify a positive statement, there seems to be a general correspondence between the virulence of the bacilli and the gravity of the case in which they are found, but there are exceptions to this. It is interesting to note that as a case progresses toward recovery a tendency has sometimes been observed toward a dimunition in the virulence of the bacilli. It has been demonstrated that the less virulent the bacillus, the smaller is the amount of the toxic proteid which it is capable of producing in cultures, this substance being replaced, according to Fränkel and Brieger, by another albuminoid product devoid of toxic properties. While other factors may be, and doubtless are, concerned in determining the severity of a case of diphtheria, it is evident that the demonstrated variability in virulence of the diphtheric bacillus affords an explanation of many of the differences observed in the onset and decline of an outbreak of diphtheria and in different epidemics of this disease. The existence of an attenuated variety of the bacillus diphtheriæ, which may, under circumstances which

we do not now understand, acquire virulence, is unquestionably of great significance in the epidemiology of diphtheria.

Roux and Yersin have brought forward a number of reasons for regarding the so-called pseudo-diphtheric bacillus (that is a bacillus resembling, if not absolutely identical with the diphtheric bacillus, in its morphology and its behavior on culture media, but incapable of killing animals) as an attenuated form of the bacillus diphtheriæ. In the two cases of apparent diphtheria referred to, in which a bacillus, which we could not distinguish from the ordinary diphtheric bacillus, save by absence of pathogenic properties when inoculated into guinea-pigs, there was a thin, grayish pseudo-membranous deposit on the tonsils, and the symptoms were of a mild character. The bacilli were present in large number and were mingled in each case with a large number of the golden pyogenic staphylococci. It would be interesting to determine whether the virulence of the diphtheric bacilli may be modified by the presence of other bacteria. Whether or not we are justified in regarding the two cases of pseudo-membranous angina referred to as genuine diphtheria cannot be decided until the status of the pseudo-diphtheric bacillus is settled.

I wish now to say a few words concerning the diagnostic value of the bacillus of diphtheria, and this will afford a convenient opportunity of touching also upon the existence of very mild cases of diphtheria and upon pseudo-membranous anginas, which are not due to the diphtheric bacillus.

While typical cases of diphtheria, especially when occurring during an epidemic, offer no especial difficulties in diagnosis, every practitioner of experience will admit that cases occur often enough which he does not know whether to call diphtheria or not. If the case is a mild one, with whitish patches on the tonsils or pharynx, which soon disappear, and constitutional symptoms are slight, he does not generally venture to make a diagnosis of diphtheria. Still the diagnosis in just this class of cases is of great importance, for such a case may be a dangerous source of infection to others.

Now we possess in the detection of the Klebs-Löffler bacillus a positive means of diagnosis of diphtheria, and it is to be considered how far this means is available to the general practitioner. The bacteriological method of diagnosis involves, first, the microscopical examination, with an oil-immersion objective, of properly stained cover-glass specimens of the suspected inflammatory exudation; second, the preparation and study of cultures from this exudation made upon suitable media, preferably Löffler's blood-serum and bouillon mixture; and third, in some cases the inoculation of a guinea-pig with the pure culture. In some cases the mere microscopical examination of cover-slip preparations from the exudation may suffice, but the diphtheric bacillus cannot be identified in this way so positively as the tubercle bacillus, for instance; and in just the class of cases where doubt as to the diagnosis is likely to exist, this procedure is most apt to prove insufficient. The examination of the cultures can be made the day following their preparation, and in nearly all cases this will afford a positive answer. The preparation of the cultures requires some training in bacteriological methods, and also a modest outfit of bacteriological apparatus. To a person thus equipped the examination offers no especial difficulties. Now, although Roux and Yersin have attempted to popularize the method, and have urged its general adoption by medical practitioners, I do not think that under existing circumstances it is likely to be widely applied in general practice. The method can be readily employed in hospitals and children's asylums, where it is calculated to be of great service, and in most large cities probably some one will be found who can be called upon to conduct such examinations. As the importance of practical training in bacteriology becomes more widely recognized in medical teaching, a larger number will enter upon the practice of their profession prepared to employ bacteriological methods of diagnosis.

The bacillus diphtheriæ has been found in a number of cases of inflammation of the tonsils and pharynx in which the exudation and the symptoms were not sufficiently characteristic to permit a positive diagnosis in any other way

than by the recognition of the specific bacillus. We do not possess sufficient information to be able to say how frequent these cases, which are generally of a very mild character, are, or how they can be diagnosticated by a merely clinical or anatomical examination. That they are not infrequent during the epidemic prevalence of diphtheria seems probable from clinical experience.

The view which has been widely advocated, that most cases of so-called follicular tonsillitis, which, as is well known, may prevail as an epidemic and may present marked but usually not dangerous constitutional symptoms, is a form of diphtheria is not supported by bacteriological examination. In these cases the diphtheric bacillus is usually absent, but under the rather vague name of follicular tonsillitis are doubtless included some cases of genuine diphtheria, generally mild, but occasionally developing into unmistakable diphtheria.

Not all pseudo-membranous inflammations of the throat are caused by the specific bacillus of diphtheria. It has been demonstrated by Wurtz and Bourges that this bacillus is absent, and that a streptococcus is present in nearly all cases of pseudo-membranous angina developing in the early stages of scarlatina, so that most cases of so-called scarlatinal diphtheria are not diphtheria at all, if we limit, as seems best, the term diphtheria to the affection caused by the Löffler bacillus. The Löffler bacillus is, however, present in the diphtheria appearing in the late stages of scarlatina and during convalescence, and it seems that scarlet fever is a predisposing cause of the development of genuine diphtheria.

In a series of cases, numbering 24, of pseudo-membranous inflammations of the tonsils, pharynx and larynx, designated at the time as diphtheria, Dr. Prudden found in all but two a steptococcus, and in none the Löffler bacillus. These cases were, for the most part, either secondary to scarlatina, measles, whooping-cough, or erysipelas, or developed under the same epidemic influence as these diseases, so that these cases probably should not be regarded as genuine diphtheria. This is the view now held by Dr. Prudden himself in his

latest publication, according to which renewed observations in cases of primary diphtheria have convinced him of the causative significance of the Löffler bacillus. Roux and Yersin, whose work has contributed largely to the present recognition of the Löffler bacillus as the cause of diphtheria, have also examined with negative result, so far as this bacillus is concerned, a few cases with pseudo-membranous deposits on the tonsils and pharynx of such a character that the clinician had no doubt of the existence of diphtheria. We must admit, therefore, that pseudo-membranous inflammations of the throat resembling diphtheria occur, both secondary to infectious diseases and apparently primary, in which the Löffler bacillus is not found. The further etiological study of these cases and their more precise characterization as to clinical history and pathological anatomy constitute a promising field of investigation. Until certain points have been cleared up by such investigation, there may be a certain amount of confusion as to the conception of diphtheria, but this affection seems to me even now sufficiently well characterized as to its symptomatology, pathological anatomy, and etiology to constitute a definite and independent disease which need not be confounded with other diseases.

A few words may be appropriately introduced here as regards the use of the terms diphtheria and diphtheritis. The term diphtheritis or diphtheritic inflammation is used in an anatomical sense to designate a certain kind of pseudo-membranous inflammation of a mucous membrane which may be produced by a variety of causes. The designation of certain other varieties of pseudo-membranous inflammations of mucous membranes as croupous and as pseudo-diphtheritic still further complicates the terminology. It is now generally recognized that it is best to limit the use of the word diphtheria to a definite disease and not to an anatomical process, thus making a distinction in the employment of the terms diphtheria and diphtheritis, the former being applied only to the disease due to a specific cause and the latter to an anatomical condition due to a variety of causes, of which the specific cause of diphtheria is only one among many. The adjective derived from diphtheria would

be diphtheric, and that from diphtheritis diphtheritic. The disease diphtheria may appear in the form of each or all of the varieties of pseudo-membranous inflammation mentioned. It has for some time been clear that the boundaries of the disease which should be called diphtheria cannot be sharply drawn save on etiological grounds. So long as these grounds were lacking the boundaries were uncertain, vague, and fluctuating. We now possess definite criteria for the recognition of the disease, and it seems to me that instead of saying that diphtheria may be caused by a variety of microörganisms, a statement which is undoubtedly true if we understand by diphtheria all pseudo-membranous inflammations of the throat, it conduces to clearness and definiteness to confine the term diphtheria to the disease caused by the Klebs-Löffler bacillus. This will not necessitate material deviation from ordinary usage. The etiological basis of classification of disease is the surest and best, and in this case it will doubtless be found to correspond to a symptomatic and anatomical entity.

The data at present at hand are insufficient to settle the burning question as to the existence, independent of diphtheria, of a disease called membranous croup, supposed to be of a purely local, non-contagious character. Not a few cases of pseudo-membranous laryngitis without membranes on the tonsils or pharynx have been examined with the result of finding the Löffler bacillus. One such case, diagnosticated by the physician as croup, will be found in the series reported by Dr. Abbott and myself. In this we detected in large numbers the diphtheric bacilli on the mucous membrane of the pharynx, although no membranous deposit was visible, and similar results have been recorded by others, so that there is no doubt that diphtheria may occur with membranous inflammation limited to the larynx. In Dr. Prudden's first series of cases there were some instances of pseudo-membranous inflammation confined to the larynx and trachea in which steptococci, but no Löffler bacilli were found, so that it is probable that pseudo-membranous laryngitis, without involvement of the tonsils or pharynx may be produced by the streptococcus. But whether or not mem-

branous croup may occur in the sense advocated as a purely local, non-contagious affection cannot be said to have been settled by bacteriological investigations.

An account of the results of the bacteriological study of diphtheria would be incomplete without some reference to pathogenic bacteria, which are frequently, although not constantly found associated with the Löffler bacillus in diphtheric exudations. These associated bacteria may be the cause of grave complications. Diphtheria is no exception to the rule that all necrotic and ulcerative processes on mucous surfaces where bacteria normally occur open the way to the invasion of pathogenic bacteria, especially to the widely distributed pyogenic streptococci and staphylococci. Mention has already been made of the probable causation of certain secondary pseudo-membranous anginas by a streptococcus. The same or apparently the same streptococcus is very commonly present in diphtheria. It is usually held to be identical with the streptococcus pyogenes. This organism, unlike the Löffler bacillus, is capable of invading the blood and tissues. The most frequent and important complication produced by this streptococcus in diphtheria is broncho-pneumonia, which develops as an aspiration pneumonia, as has been shown by the investigations of Prudden and Northrup. The common pus-producing bacterium, the staphylococcus pyogenes aureus is, next to the streptococcus, the most common pathogenic bacterium complicating diphtheria. It is to the invasion of these secondary bacteria that such complications of diphtheria as acute ulcerative endocarditis, suppuration of lymphatic glands, inflammations of serous membranes, and erysipelas are referable.

A matter which, although not new, has attracted much attention in recent years, may prove to be of such importance in the etiology of diphtheria that I will direct your attention to it for a few moments. Evidence has been brought forward intended to show that diphtheria may be communicated to human beings by domestic animals afflicted with this disease. The animals chiefly concerned are cattle, cats and fowls. There have been reported in England during the last decade epidemics of diphtheria in which the evidence is strong that

the diphtheric germ was conveyed in milk. There are two theories as to these milk epidemics. One is that the diphtheric virus got into the milk from persons affected with diphtheria, the other is that the cows yielding the milk were affected with diphtheria. This second daring hypothesis Klein has attempted to support by experiment. He claims that by the inoculation of two cows subcutaneously on the shoulder with a broth culture of the bacillus diphtheriæ he has succeeded in producing genuine infection with the appearance of vesicles and pustules on the udders and the elimination of the specific bacilli by the milk. These experiments should be received with great caution, as they are in opposition to all that we know concerning the exclusively local development of the bacilli at the point of inoculation. We possess no satisfactory evidence that cattle are ever affected with a natural disease identical etiologically with human diphtheria, although it is known that an affection sometimes called diphtheria may appear in calves.

That cats may acquire diphtheria and may be a means of transmitting the disease to human beings is a widely-spread belief. Medical literature contains many instances in which on the one hand, cats appear to have contracted a disease by eating substances contaminated with the discharges from diphtheric persons; and, on the other hand, children seem to have become infected with diphtheria by handling sick cats. Noah Webster, in his curious book on *Epidemic and Pestilential Diseases*, published at the end of the last century, noted the coincidence of cat distempers with malignant angina. In the recently published *Annual Report of the Local Government Board of England*, Klein has brought together the evidence to be found on this point. Inasmuch as cats are among the animals most susceptible to inoculation with cultures of the Löffler bacillus, acquiring a disease resembling human diphtheria, there is no *a priori* reason why they may not be the subjects of a natural disease etiologically identical with diphtheria. But the possibility of the experimental production of a disease in an animal is no proof of the natural occurrence of such disease; and thus far there is not satisfactory evidence that diphtheria occurs as a natural

disease in cats. What is necessary to settle this question is to make careful bacteriological studies in cases of suspected diphtheria in cats. The matter is of sufficient interest and importance to merit careful study, and we should be glad of the opportunity of making examinations in suitable cases which may come to the notice of physicians in this vicinity.

Pigeons also are susceptible to inoculation with the Löffler bacillus, and it is well-known that a membranous inflammation of the mouth, fauces, and trachea occurs as a destructive epidemic in chickens, turkeys, pigeons and other birds. This so-called diphtheria of fowls has not, however, been found to be caused by the same microörganism which causes human diphtheria, so that notwithstanding some rather striking observations according to which human beings have appeared to contract diphtheria from fowls, there is no positive proof of the dissemination of genuine diphtheria in this way. It may be that human beings may become infected by the germs producing the so-called diphtheria in domestic animals, but if so, there is no proof that the disease produced is etiologically identical with the disease caused by the Löffler bacillus.

We have now passed over, gentlemen, in rapid survey, some of the leading factors concerned in the causation of diphtheria. The limits of an address do not permit an exhaustive consideration of the subject even from the bacteriological point of view. Many circumstances of great importance in the etiology of diphtheria, such as the influence of unsanitary surroundings, particularly those of a domestic character, and the often dominant *role* of school attendance upon the dissemination of the disease could not be considered. These, however, are etiological factors which can be more profitably discussed from an epidemiological than a bacteriological point of view.

I have already made such demands upon your patience that I have not left myself sufficient time for any adequate consideration of the prophylaxis and treatment of diphtheria —subjects, indeed, which would furnish ample material for a

separate discourse. I am glad to see that the subject of the treatment of diphtheria is to be presented in a special paper before this meeting. I cannot refrain, however, from directing your attention to a few of the general principles controlling methods of prevention and of treatment of diphtheria, and from pointing out the directions in which our increased knowledge of the causation of diphtheria leads us in our search for more effective measures to these ends.

The very fact that we are no longer groping in the dark, but that we know the enemy, his strength and his weakness, should inspire our courage and hope, should make us forge new weapons and sharpen our old ones, and should point out where to ward off attack and where to force the battle.

The possibility of making an early diagnosis of diphtheria by the aid of bacteriological examinations enhances the chances of success in coping with this disease, both in prevention and in treatment, and, as already intimated, provision should be made in hospitals and children's asylums for making such examinations.

Inasmuch as the diphtheric bacilli are present only in the false membranes and other local products of the disease at the site of infection, and are distributed outside of the body primarily through these, it is apparent that the patient should be strictly isolated; that unnecessary fabrics and other objects, especially such as cannot be readily disinfected, should be first removed from the room where the patient is placed; that care should be taken to prevent, as far as possible, the soiling of the person and clothing of the patient, of the attendants, and of the physician, as well as that of other objects in the room, with the discharges of the patient; that opportunity should not be afforded for the desiccation of these discharges, which then may contaminate the air, and that efficient measures of disinfection of the room and of all objects which by any possibility can become infected should be employed. That the enforcement of the measures indicated is capable of restraining the spread of the disease, even in crowded infants' asylums and hospitals, has already been demonstrated by actual experience. They require for their accomplishment education on the part of the community,

of physicians, and of sanitary authorities in the principles of disinfection, and an intelligent appreciation of the dangers to be guarded against. I seize this occasion, as I have others, to urge the importance in cities of public disinfecting establishments, constructed according to improved modern principles, and of a corps of men in the employment of boards of public health, trained in proper methods of disinfection.

The length of time that the patient should be quarantined depends evidently upon the duration of the period in which active diphtheric bacilli remain on the mucous surfaces attacked. As to this point we possess some definite information, which shows that the period varies within wide limits. In some cases the bacilli can no longer be found after the false membranes have completely disappeared. In many cases they vanish within three or four days after the local inflammation has subsided, but they have been found as long as fourteen days after the inflammation has gone, and when the mucous membrane appeared healthy. In a case reported by Löffler, the bacilli were found three weeks after the return of the temperature to the normal, and were present for a month altogether in a state capable of carrying infection. It is evidently not possible to set a precise limit for the period of isolation of the patient. Löffler suggests that the patient should not be permitted to mingle with others or to return to school for at least eight days after the disappearance of all local manifestations, and he reckons four weeks from the beginning of the disease as the period for keeping the children out of school. Where it is possible to do so, the length of this period can be controlled by bacteriological examinations of the mucous membrane of the throat.

We have thus far considered the patient as the immediate source of infection. The evidence already mentioned in favor of the occasional dissemination of the diphtheric virus through the milk suggests at once the importance of controlling, not only the condition of the milk as received for distribution, but also of inspecting the sources of milk supply. Evidently milk should not be permitted to be sold from

dairies attached to households where there are cases of diphtheria.

It does not seem to me permissible to throw out altogether the possibility of the conveyance of diphtheria by domestic animals, especially by cats, which are likely to be fondled by children even more when the animals are sick than when they are well.

In considering what can be done to render children less vulnerable to diphtheria, and to ward off an attack after exposure to the disease, the question arises, what conditions of the individual we may regard as predisposing causes. Clinical experience, as well as experiments upon animals, indicate that morbid states of the mucous membrane of the throat, such as ordinary catarrhal inflammations, swollen tonsils, sensitiveness to "catching cold," the existence of measles and scarlatina, are predisposing factors. At all times, but especially during the epidemic prevalence of diphtheria, it is important to hold in check these morbid states as far as possible. Experiments upon animals would seem to indicate that some lesion of the mucous membrane is essential for the lodgment and multiplication of the diphtheric bacilli, but it would be entirely unjustifiable to transfer directly to human beings the results of these experiments without warrant from clinical experience, and while this experience shows the importance of such lesion, it also shows that perfectly healthy children may be attacked by diphtheria, so that we have no right to assert that in human beings infection with the diphtheric bacilli cannot occur without pre-existing alteration of the mucous membrane. The frequency and readiness with which the tonsils become the seat of the diphtheric process may be explained by the peculiar anatomical structure of these parts, as has been shown by the researches especially of Stöhr and of Hodenpyl. The rarefaction of the covering epithelium and the emigration of leucocytes to the surface found as a normal condition, seem to render the tonsils particularly vulnerable to the lodgment of the diphtheric bacilli; and the lymphatic structures, here normally laid almost bare, are favorable for the absorption of the toxic products of the bacilli, as has been pointed out

in the recent interesting paper of Hodenpyl, "On the Anatomy and Physiology of the Faucial Tonsils."

The prophylactic value, in persons liable to exposure to diphtheria, of cleanliness of the teeth and mouth and of the frequent use of weak antiseptic mouth-washes, nasal douches, and gargles, is worthy of the attention of physicians. For this purpose Löffler recommends aromatic waters, weak sublimate solutions [1 : 10000 to 1 : 15000], or, perhaps better, solutions of mercuric cyanide [1 : 8000 to 1 :10000] also, chloroform water, chlorine water [1 : 1100] thymol, [1 : 500 parts of 20 per cent. alcohol]. The use of some of these solutions evidently involves danger of poisoning in children unless special precautions are taken.

The suggestion recently made by Dr. Jacobi, that, in addition to caring for those sick with diphtheria, places of refuge should be provided for the temporary stay of children sent from home to escape infection, seems practical and calculated to meet the circumstances of many families.

The dominant role often played by schools in the spread of diphtheria throughout a community renders especially urgent the introduction of a system of daily medical inspection of the schools.

The importance of letting air and sunlight into dark, damp dwellings, and of attending in general to matters of domestic sanitation, is a lesson plainly to be drawn from the history of such places as nests of diphtheria.

If the researches relating to the etiology of diphtheria which have been so fruitful in recent years have not added to the list of agents—whose name is legion—employed in the treatment of this disease, they have given precision to the indications for treatment. From what has been said concerning the localization of the diphtheric bacilli, and the peculiar characters of the toxic substances produced by them, it is apparent that the strongest indications exist, on the one hand, for the earliest possible local treatment by germicides, and, on the other, for the destruction of the poison in the system, and, in the absence of any antidote,

for supporting measures of treatment which shall enable the body to withstand the effects of the poison.

The superficial situation of the specific bacilli in diphtheria seems to render this disease especially favorable for effective local antiseptic treatment, but the difficulties encountered in actually destroying the germs in the diphtheric deposits, even when these are accessible to local applications, emphasize the fact that the obstacles to thorough disinfection within the human body are exceedingly great. Many of our most powerful antiseptics, when they come into contact with the tissues and fluids of the body form precipitates which render them largely inert, and for this and other reasons they penetrate but slowly or not at all beyond a very superficial extent. But above all we are hampered by the fact that nearly all disinfectants are many times more poisonous to the cells of the human body than they are to bacteria.

But notwithstanding the difficulties mentioned, and still others suggest themselves, it has been shown both by bacteriological examinations and by clinical experience that local disinfectant applications in diphtheria are useful and may cause the specific bacilli to disappear. An important experimental study of the action upon the diphtheric bacilli of many germicides and agents used in treating diphtheria has been recently published by Löffler, who endeavored to imitate as far as possible in test-tube experiments the conditions present in the mucous membrane when affected with diphtheria. I can only refer you to Löffler's work and his recomdations. Any attempt to consider here therapeutic agents would lead us far beyond the limits of our subject as well as of our time.

Even if it were within the power of the physician to bring about the complete destruction of the bacilli diphtheriæ after the disease has taken a firm hold, he would nevertheless in many cases be called upon to combat the effects of the toxæmia resulting from the absorption of the toxic albumen already produced by the bacilli. In this respect there is an analogy between diphtheria and tetanus. In both of these diseases the specific bacteria develop only locally at the site of infection, where they produce substances of extraordinary poison-

ous power which enter the circulation. In the case of tetanus we are familiar with the fact that even the complete removal of the infected part will not prevent a fatal issue after a certain amount of poison has been produced and has entered the system. Experiments already mentioned have shown that animals may be killed by the injection of an amount so small of the toxic albumen produced by the diphtheric bacilli that for several days no symptoms are manifested. The physician certainy cannot neglect the dangers of intoxication by such a substance as this.

The interesting experiments of Behring and Kitasato upon the production of immunity against tetanus and diphtheria encourage us to hope that we may in time come into the possession of direct antidotes to the chemical poisons of these diseases. These experiments have shown that the blood and the blood serum of animals naturally or rendered artificially immune against diphtheria, possess the remarkable property of neutralizing or destroying the toxic substances produced by bacilli diphtheriæ, and that immunity depends upon this property. The same is true of tetanus. Whether or not any therapeutic application in human beings can be successfully made of this property of the blood of immune animals, has not yet appeared.

Failing any such antidote, it should be the aim of the physician to assist nature to withstand the poison by supporting the strength of the patient in every way possible by remedies and food.

I have attempted, gentlemen, in this address to show, although necessarily in an imperfect and fragmentary manner, that the discovery of the bacillus diphtheriæ and the study of its properties have rendered our knowledge of diphtheria in many ways more accurate and fuller, have settled many questions of controversy, and have dissipated some errors. The new light has not yet penetrated into all of the dark corners, but when we consider what has been gained in less than a decade, we are justified in expecting that here also obscurity will disappear, and that diphtheria will become in all respects one of the best understood, and, we may hope, one of the most successfully combated of the grave infectious diseases.